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Bound Water as a Tool to Detect Soluble Amyloid Oligomers and Amyloid Protofibrils, the Early Stage of Development of the Alzheimer's Disease

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We investigated the fundamental molecular-level behavior of water molecules adjacent or very close to the surface of amyloid peptides, soluble oligomers and protofibrils. The foucus was on prospecting a reliable means to predict, measure and interpret the magnetic behavior of such water molecules, especially to differentiate their magnetic behavior from that of other, more bulk-like molecules. The long term goal of this will be developing a diagnostic method to enable magnetic resonance relaxation measurements to reveal the nature of the surfaces to which those water molecules are associated, and hence to provide a probe of the extent of tissue damage in the early stage of development of conformational diseases, such as the Alzheimer's disease.

1 Introduction

At structural level, proteins display both binding (hydrophilic) and unbinding (hydrophobic) sites for water molecules. Most of hydrophobic moieties are buried inside the structure when proteins are in native states. They become exposed when proteins unfold (or misfold), which weakens the effective interaction of surrounding water with the protein surface[1]. Recent studies[2] suggest that isomers bearing pathological defects, i.e. proteins exhibiting poorly dehydrated backbone hydrogen bonds (dehydrons)[3,4], are characterized by an average energy of hydration that is also significantly bellow that corresponding to native proteins. Though these structural defects generally interact with nearby water, the entropy of this water is unexpectedly large and the residence time much shorter than at hydrophilic sites[2]. Thus, both unfolded/misfolded and pathogenic proteins exhibit an increased number of surface patches where the local water is less structured and has an increased mobility[5,6], reminiscent of the bulk solvent. Moreover, energetic considerations suggest that isomers with considerable bulk-like hydration tend to aggregate[7]. Here, we summarize the results of our initial studies which suggest that different morphological states of aggregated isomers differ by hydration distribution profiles and water magnetic resonance (MR) signals. The results help explain the MR contrast patterns of amyloids, a subject of long controversy, and suggest a new approach for identifying unusual protein aggregation related to disease.

Extracellular amyloid β (Abeta) deposits are prominent and universal Alzheimer's disease (AD) features but plaque abundance does not reflect the actual degree of the neuronal injury in AD patients[8]. The incipient assemblies formed by Abeta peptides inside the cell, such as soluble oligomers and fibrillar tangles, also have potent neurotoxic activities, and in fact, may be the proximate effectors of the neuronal injury and death occurring in AD[8].

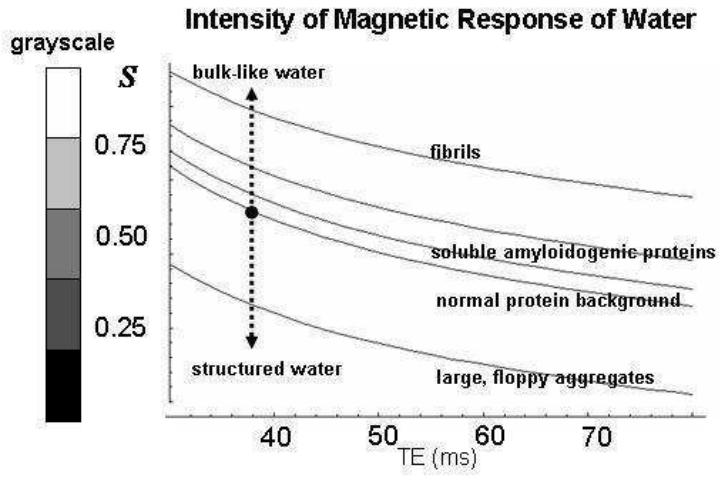

Figure 1. The relative change in pixel intensity corresponding to distributions of constrained water in local environments containing normal protein background, soluble amyloidogenic anssemblies, protofibrils and large protein aggregates.

Thus, the most visible manifestation of amyloid accumulation, i.e. extracellular Abeta plaques, could actually be a defense mechanism employed to avoid serious tissue degradation while the major toxic effects to the gray and white matter neurons are mediated by soluble Abeta composites and protofibrils. Therefore, developing strategies to detect in vivo the Abeta structures at an early stage are crucial for treating, inhibiting the progression of disease and preventing some of the devastating effects of AD.

2 Methods

Based on the scaled particle theory[9], we derived a mathematical algorithm that describes the recompartmentalization of water following the addition of test isomers in the local environment and the association of these isomers in composites of given structures (i.e. oligomers, protofibrils and large protein aggregates). The mathematical equations for the recompartmentalization of water are given in terms of the local hydration fraction (η) and packing density (ρ) of the newly formed molecular assembly, as described previously[7]. Then, we use standard relaxometry equations[7] to correlate the intensity (S) of the magnetic relaxation response of water with η and ρ for each structural archetype (single isomers, oligomers, protofibrils and large aggregates). Based on this model, we investigated the relationship between the intensity of the magnetic response, the amount of constrained water in the local volume and morphological characteristics of the protein system. The predicted magnetic signal intensity for these systems is compared to that corresponding to native protein background (control).

3 Results and Discussion

The present study suggests that a cellular environment containing pathogenic proteins and distinct morphological structures formed by the association of these proteins differ from normal protein background by the quantity of water structured at interfaces. The reorganization of hydration water molecules leads implicitly to a redistribution of water molecules among the characteristic clusters of the relaxation times[2,6]. Normally, such differences lead to distinct MRI signals. The fact can be inferred from Fig. 1 where we show generic curves of the relative change in pixel intensity corresponding to the magnetic response of constrained water in various local environments (i.e. normal protein background, test isomers, oligomers, protofibrils, large protein aggreagtes). We can notice that the hyperintensity curve corresponding to compact aggregates is the closest to the pixel intensity of bulk water. Therefore, regions containing small compact aggregates are likely to show brighter than the normal protein gray background on MR images. On the contrary, the formation of large, floppy protein aggregates by including large amounts of test isomers and caged water, leads to the occurrence of hypo-intensity on the characteristic MR images. Hence the MR images of such microscopic environments will show darker on the grayscale. The characteristic magnetic sensitivity for a system containing additional test isomers in a morphological state as described in above is represented in Fig. 1 by the bottom curve. We must note that this hypo-intensity signal is apart from the contrast produced by the presence of iron in plaques[10–14]. The present study shed light on a current controversy, namely that amyloids can display both dark and bright spots when compared to the normal, gray background tissue on MR images[10,11]. In addition, our findings suggest that the bright spots are more likely to correspond to amyloids in their early stage of development.

4 Concluding Remarks

The present results are in support of existing experimental data[10,13,14] showing that the presence of iron in amyloid plaques is not always decisive for detecting the AD. We have presented compelling theoretical evidence that placing additional constraints on water dynamics (i.e., caging water) and/or redistribution of constrained water fractions also play a significant role in correlating the intensity of the MR signal with the amyloid load. Our results help to better understand various biophysical mechanisms that set the MR signal of water surrounding amyloidogenic proteins and their model aggregates. Our study may prove useful in generating new testable statements on circumstances related to the presence of amyloidogenic proteins in a given aqueous environment. Progress in understanding the chemistry effects induced by such molecular entities on dynamics of surrounding water in combination with data from new MR spectroscopic methods for determining the overexpression of abnormal proteins and their state of association in the cell can help designing efficient MR imaging protocols to be used in detecting the early molecular alterations in amyloidogenic diseases.

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